DETAILED ACTION

The preliminary amendment filed on 25 September 2005 in which claims 1-9 were cancelled, and claims 10-18 were newly added, is acknowledged.

Claims 10-18 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/EP2005/051364 filed on 23 March 2005 and claims priority to EPO foreign application 04101199.0 filed on 23 March 2004. A certified copy of the foreign priority document in English has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 25 September 2006 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are grouped as follows:

(1) Compounds of the formula shown in instant claim 10;

(2) Various Gram-negative bacterium, enumerated in claim 12; and

(3) Various infections, enumerated in claims 13, 15 and 17.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: claim 10.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not any particular technical feature makes a "contribution" over the

prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step.

The common technical feature is the ethyl-α-mannopyranoside compound. This element cannot be a special technical feature under PCT Rule 13.2 because the element is shown in the prior art.

In this case, journal publication by Nagahori *et al.* (PTO-892, Ref. U) teaches the inhibition potencies of various mannopyranosides towards binding by *E. coli*. Ethyl mannopyransoide is shown in Table 3 (p. 839).

As a result, no special technical features exist because the inventions fail to make a contribution over the prior art with respect to novelty and inventive step. In conclusion, there is a lack of unity of inventions, and therefore restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Daniel Morath on 31 July 2008, a provisional election was made for (1) heptyl-D-α-mannopyranoside, wherein R_0 = O and R_1 = n-pentyl, (2) *Escherichia coli*, and (3) urinary tract infection. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 10-14 will be examined herein to the extent they read on the elected species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Nagahori *et al.* (PTO-892, Ref. U), journal publication by Choudhury *et al.* (PTO-892, Ref. V), and published symposium abstract by Bouckaert (PTO-892, Ref. W).

Nagahori *et al.* teach the inhibition of adhesion of type 1 fimbriated *Escherichia coli* to a various mono-, di- and trivalent mannosides. Many bacteria, including pathogenic ones, express carbohydrate-specific adhesion on their fimbriae. These fimbrial adhesins are often implicated in the initial recognition/binding of bacteria to host cells or persisting colonization of bacteria on certain host cell surfaces. The mannose-specific adhesion of type 1 fimbriated *E. coli* (known as the FimH protein) is known to cause common urinary tract infection (p. 836, column 1, paragraph 1). High-affinity ligands for these adhesins may be useful as therapeutics for preventing or mitigating pathological symptoms (p. 836, column 1, paragraph 2). Compounds that were tested for inhibition towards binding of ^{125}I-Man_{21}-ALK-HSA to *E. coli* include methyl-mannopyranoside, ethyl-mannopyranoside, p-nitrophenyl-mannopyranoside, as well as

trivalent mannose compounds, divalent mannose compounds, neoglycoproteins, and dendrimers (p. 839, Table 3 and Table 4; p. 840 Table 5). The results of their study indicated that the presence of the α-mannose configuration enhances the affinity of the compound tremendously (p. 840, subheading "Discussion", paragraph 1). It appears that the β-oriented aglycon does not make good contact with the hydrophobic surface (p. 841, column 1, first full paragraph). The results also indicate that either a long aliphatic chain or an aromatic ring immediately next to the mannose sugar produces the best inhibitors (p. 836, paragraph 2). Nagahori *et al.* conclude that in designing a potential inhibitor of *E. coli* adhesion that is medically applicable, it is obviously prudent to incorporate a long aliphatic chain or an aromatic residue immediately next to mannose (p. 841, column 2, second full paragraph). The affinity can also be further enhanced by multivalency, such as by using dendrimers or neoglycoproteins.

With respect to the limitation of instant claim 11, the terms pilus and fimbriae are commonly used interchangeably (Salyers *et al.*, PTO-892, Ref. X).

Nagahori *et al.* does not explicitly teach the mannopyranoside species, heptyl-α-D-mannopyranoside, elected by the applicants. However, as discussed above, Nagahori *et al.* do explicitly indicate that a potential inhibitor of *E. coli* adhesion that is medically applicable would incorporate a long aliphatic chain or an aromatic residue immediately next to mannose (p. 841, column 2, second full paragraph).

Furthermore, Choudhury *et al.* teach an x-ray structure of the FimC-FimH chaperone-adhesin complex from uropathogenic *Escherichia coli*. The structure shows a pocket capable of accommodating a mono-mannose unit located at the tip of the

FimH lectin domain (p. 1062, column 3; p. 1063, Fig. 1B). In an attempt to further understand the lectin-substrate binding, a molecule of cyclohexylbutanoyl-*N*-hydroxyethyl-D-glucamide (C-HEGA) is bound in the pocket (p. 1062, column 3; p. 1064, Fig. 3A). The C2, C3, C4 and C6 hydroxyl groups of C-HEGA are enclosed within the pocket, whereas the cyclohexylbutanoyl-N-hydroxyethyl groups point out from the pocket (p. 1062, column 3). These results indicate the importance of the C2, C3, C4 and C6 hydroxyl groups of mannose in binding, suggesting that alteration of these groups decreases binding and that alterations to the mannose structure can only be made at C1. Moreover, Bouckaert *et al.* teach interactions of FimH with D-mannopyranoside by x-ray crystallography. Their crystal structure identified an extensive hydrophobic patch surrounding the mannose binding crevice (abstract C2.17). Mutation of the hydrophobic interactions generally did not result in loss of interaction with D-mannopyranoside.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagahori *et al.*, concerning medically applicable inhibitors of E. coli adhesion that incorporates an α-linked long aliphatic chain or an aromatic group at the anomeric position of mannose, with the teachings of Choudhury *et al.*, regarding the importance of the C2, C3, C4 and C6 hydroxyl groups of mannose in E. coli binding as deduced from the x-ray structure thereby indicating that modifications to mannose can only be made at C1, with the teachings of Bouckaert *et al.*, regarding the presence of a substantial hydrophobic binding site located within the binding pocket. It would have been *prima facie* obvious for a skilled artisan to use the

information disclosed by Nagahori *et al.*, Choudhury *et al.*, and Bouckaert *et al.* to design a medically applicable inhibitor of *E. coli* adhesion that contains a long aliphatic chain at the anomeric position, such as heptyl-α-D-mannopyranoside. One of ordinary skill in the art would know that a composition comprising an *E. coli* adhesion inhibitor can thus be used in a method to treat a subject infected with uropathogenic *E. coli*, which is involved in urinary tract infection. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagahori *et al.*, that high affinity ligands for bacterial adhesins may be useful as therapeutics for preventing or mitigating pathological symptoms (p. 836, column 1, paragraph 2).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Applicants' data in Tables 1-3 with respect to K_D values and $\Delta G°$ values of the various compounds have been considered. It is noted that some of compounds exhibit values that are drastically different from methyl-mannopyranoside and ethyl-mannopyranoside. However, no conclusion can be drawn regarding the significance of the data as no statistical analysis is shown.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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